1. NAME OF THE MEDICINAL PRODUCT

Haemocomplettan® P 1g
Powder for solution for injection / infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Haemocomplettan is presented as a powder for solution for injection or infusion for intravenous administration containing 1g human fibrinogen per vial.

The product contains 20 mg/ml human fibrinogen after reconstitution with 50 ml water for injections for Haemocomplettan P 1g.

The content of clottable fibrinogen is determined according to PH. Eur. monograph for human fibrinogen.

Excipients recognised to have a known effect: Sodium up to 164 mg (7.1 mmol) per 1g fibrinogen.
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of bleeding in patients with congenital hypo-, or afibrinogenaemia with bleeding tendency.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

Posology
The dosage and duration of the substitution therapy depend on the severity of the disorder, location and extent of bleeding and the patient's clinical condition.

The (functional) fibrinogen level should be determined in order to calculate individual dosage and the amount and frequency of administration should be determined on an

individual patient basis by regular measurement of plasma fibrinogen level and continuous monitoring of the clinical condition of the patient and other replacement therapies used.

Normal plasma fibrinogen level is in the range of 1.5 – 4.5 g/l. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l.

In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.

Initial Dose
If the patient's fibrinogen level is not known, the recommended dose is 70 mg per kg of body weight (BW) administered intravenously.

Subsequent Dose
The target level (1 g/l) for minor events (e.g. epistaxis, intramuscular bleeding or menorrhagia) should be maintained for at least three days. The target level (1.5 g/l) for major events (e.g. head trauma or intracranial haemorrhage) should be maintained for seven days.

$$\text{Dose of fibrinogen (mg/kg body weight)} = \frac{\text{[Target level (g/l) - measured level (g/l)]}}{\text{0.017 (g/l per mg/kg body weight)}}$$

Dosage for neonates, infants and children
Limited data from clinical studies regarding the dosage of Haemocomplettan P in children are available.
Resulting from these studies, as well as from long lasting clinical experience with fibrinogen products, dosage recommendations in the treatment of children are the same as for adults.

Method of Administration
Intravenous infusion or injection.
Haemocomplettan should be reconstituted according to section 6.6. The reconstituted solution should be warmed to room or body temperature before administration, then injected or infuseed slowly at a rate which the patient finds comfortable. The injection or infusion rate should not exceed approx. 5 ml per minute.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

There is a risk of thrombosis when patients with congenital deficiency are treated with human fibrinogen, particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.

In patients with a history of coronary heart disease or myocardial infarction, in patients with liver disease, in peri- or post-operative patients, in neonates, or in patients at risk of thromboembolic events or disseminated intravascular coagulation, the potential benefit of treatment with human plasma fibrinogen should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.

If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.

In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions have been observed, but there is currently no data with fibrinogen.

Important information about specific excipients of Haemocomplettan
Haemocomplettan contains up to 164 mg (7.1 mmol) sodium per 1g fibrinogen. This correlates with 11.5 mg (0.5 mmol) sodium per kg body weight of the patient if the recommended initial dose of 70 mg/kg body weight is applied. To be taken into consideration by patients on a controlled sodium diet.

Virus safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and hepatitis B) should be considered for patients in regular/repeated receipt of human fibrinogen products.

It is strongly recommended that every time that Haemocomplettan is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human plasma fibrinogen products with other medicinal products are known.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal reproduction studies have not been conducted with Haemocomplettan (see section 5.3). Since the active substance is of human origin, it is catabolized in the same manner as the patient's own protein. These physiological constituents of the human blood are not expected to induce adverse effects on reproduction or on the fetus.

The safety of human plasma fibrinogen products for use in human pregnancy has not been established in controlled clinical trials.

Clinical experience with fibrinogen products in the treatment of obstetric complications suggests that no harmful effects on the course of the pregnancy or health of the fetus or the neonate are to be expected.

Lactation
It is unknown whether Haemocomplettan is excreted in human milk. The safety of human plasma fibrinogen products for use during lactation has not been established in controlled clinical trials.
A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Haemocomplettan therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data regarding effects of Haemocomplettan on fertility.

4.7 Effects on ability to drive and use machines

Haemocomplettan has no influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Allergic or anaphylactic type reactions have been uncommonly observed. The events reported in association with allergic/anaphylactic reactions include generalized urticarial, rash, dyspnoea, tachycardia, nausea, vomiting, chills, pyrexia, chest pain, cough, blood pressure decreased, and anaphylactic shock (see section 4.4).

The risk of thromboembolic events (TEE) following the administration of fibrinogen concentrate (see section 4.4.) as determined in clinical trial is further described in the table below.

Pyrexia has been very commonly observed.

b. Tabulated list of adverse drug reactions (ADRs)

This table combines the adverse reactions identified from clinical trials and post marketing experience. Frequencies presented in the table have been based on pooled analyses across two company sponsored clinical trials performed in aortic surgery with or without other surgical procedures (BI3023-2002 and BI3023_3002) according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) or unknown (cannot be estimated from the available data).

The calculated frequency is based on crude incidence rates without considering the frequency of the comparator arm. It should be noted that in the clinical trials included in the analysis, the incidence of TEEs was higher in the placebo arm. In view of the fact that these trials were conducted in only the narrow population of aortic surgery with or without other surgical procedures, adverse drug reaction rates observed in these trials may not reflect the rates observed in clinical practice and are unknown for clinical settings outside the studied indication.

MedDRA SOC	**Undesirable effects**	**Frequency** **(In aortic surgery with or without other surgical procedures)**
General Disorders and Administration Site Condition	Pyrexia	Very common
Immune System Disorder	Allergic or anaphylactic reactions	Uncommon
Vascular Disorder	Thromboembolic events*	Common**

** Isolated cases have been fatal.*
*** Based on results of two clinical trials (aortic surgery with or without other surgical procedures), the pooled incidence rate of thromboembolic events was lower in fibrinogen treated subjects compared with placebo (see 4.8.c).*

c. Description of selected adverse reactions (ADRs)

BI3023_2002 study is a Phase II study of fibrinogen concentrate human (FCH) compared with placebo (saline) in subjects with acute bleeding while undergoing aortic repair surgery. BI3023-3002 study is a Phase III study of FCH versus placebo (saline) to control bleeding during complex cardiovascular surgery. In BI3023_2002 study (N=61), TEE occurred

similarly in fibrinogen and placebo groups. In BI3023_3002 study (N=152), TEE occurred more frequently in the placebo group than in the FCH group.

Pooled incidence rate of listed ADRs from company sponsored clinical trials (BI3023_2002 and BI3023_3002)

ADRs	**FCH (N=107)**	**Placebo (N=106)**
Pyrexia	11 (10.4%)	5 (4.7%)
Thromboembolic events	8 (7.4%)	11 (10.4%)
Allergic or anaphylactic reaction	1 (0.9%)	0

For safety with respect to transmissible agents, see section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated (see 4.2).
In case of overdosage, the risk of development of thromboembolic complications is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group***:*** antihaemorrhagics**,** human fibrinogen,
ATC code: B02B B01

Human fibrinogen (coagulation factor I), in the presence of thrombin, activated coagulation factor XIII (F XIIIa) and calcium ions, is converted into a stable and elastic three-dimensional fibrin haemostatic clot.

The administration of human fibrinogen provides an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with fibrinogen deficiency.

The pharmacokinetic study evaluated the single-dose pharmacokinetics and maximum clot firmness (MCF) in subjects with afibrinogenaemia. MCF was determined by thromboelastometry (ROTEM) testing. MCF was measured to demonstrate functional activity of replacement fibrinogen when a fixed dose of Haemocomplettan® was

administered. Clot firmness is a functional parameter that depends on: activation of coagulation, fibrinogen content of the sample and polymerisation/crosslinking of the fibrin network. Thromboelastometry has been shown to be a functional marker for the assessment of fibrinogen content and for the effects of fibrinogen supplementation on clinical efficacy.

For each subject, the MCF was determined before (baseline) and one hour after the single dose administration of Haemocomplettan®. Haemocomplettan® was found to be effective in increasing clot firmness in patients with congenital fibrinogen deficiency (afibrinogenaemia) as measured by thromboelastometry. The study results demonstrated that the MCF values were significantly higher after administration of Haemocomplettan® than at baseline (see below table). The mean change from pre-infusion to 1 hour post-infusion was 8.9 mm in the primary analysis (9.9 mm for subjects <16 years old and 8.5 mm for subjects ≥16 to <65 years old). The mean change in MCF values closely approximated the levels expected from adding known amounts of fibrinogen to plasma in vitro.

Maximum clot firmness [mm] (Intention to treat population)

Time point	**N**	**Mean ±SD**	**Median (range)**
Pre-infusion	13	0±0	0 (0–0)
1 hour post-infusion	13	10.3±2.7	10.0 (6.5–16.5)
Mean change (primary analysis)[a]	15[b]	8.9±4.4	9.5 (0–16.5)

mm = millimetre
[a] p-value was <0.0001.
[b] The mean change was set to 0 for 2 subjects with missing MCF data.

Adverse reactions encountered during the clinical trials are outlined in section 4.8 Undesirable effects.

5.2 Pharmacokinetic properties

Human plasma fibrinogen is a normal constituent of the human plasma and acts like endogenous fibrinogen. In plasma, the biological half-life of fibrinogen is 3 to 4 days. Regarding degradation Haemocomplettan behaves like the endogenous fibrinogen.

Haemocomplettan is administered intravenously and is immediately available in a plasma concentration corresponding to the dosage administered.

A pharmacokinetic study evaluated the single-dose pharmacokinetics before and after administration of human fibrinogen concentrate in subjects with congenital afibrinogenaemia. This prospective, open label, uncontrolled, multicenter study consisted of 5 females and 10 males, ranging in age from 8 to 61 years (2 children, 3 adolescents, 10 adults). The median dose was 77.0 mg/kg body weight (range 76.6 – 77.4 mg/kg).

Blood was sampled from 15 subjects (14 measurable) to determine the fibrinogen activity at baseline and up to 14 days after the infusion was complete. In addition, the incremental *in*

vivo recovery (IVR), defined as the maximum increase in fibrinogen plasma levels per mg/kg body weight dosed, was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.7 (range 1.30-2.73) mg/dl per mg/kg body weight. The following table provides the pharmacokinetic results.

Pharmacokinetic results for fibrinogen activity

Parameter (n=14)	Mean ± SD	Median (range)
$t_{1/2}$ [h]	78.7 ± 18.13	77.1 (55.73-117.26)
C_{max} [g/l]	1.4 ± 0.27	1.3 (1.00-2.10)
AUC for dose of 70 mg/kg [h•mg/ml]	124.3 ± 24.16	126.8 (81.73-156.40)
Extrapolated part of AUC [%]	8.4 ± 1.72	7.8 (6.13-12.14)
Cl [ml/h/kg]	0.59 ± 0.13	0.55 (0.45-0.86)
MRT [h]	92.8 ± 20.11	85.9 (66.14-126.44)
V_{ss} [ml/kg]	52.7 ± 7.48	52.7 (36.22-67.67)
IVR [mg/dl per mg/kg body weight]	1.8 ± 0.35	1.7 (1.30-2.73)

$t_{1/2}$ = terminal elimination half-life
h = hour
C_{max} = maximum concentration within 4 hours
AUC = area under the curve
Cl = clearance
MRT = mean residence time
V_{ss} = volume of distribution at steady state
SD = standard deviation
IVR = in vivo recovery

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity and safety pharmacology.

Preclinical studies with repeated dose applications (chronic toxicity, cancerogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin,
L-arginine hydrochloride,
sodium hydroxide (for pH adjustment),
sodium chloride,
sodium citrate.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, diluents, or solvents except those mentioned in section 6.6. A standard infusion set is recommended for intravenous application of the reconstituted solution at room temperature.

6.3 Shelf life

5 years.

The physico-chemical stability for the reconstituted product has been demonstrated for 8 hours at room temperature (max. +25 °C). From a microbiological point of view the product should be used immediately following reconstitution. If the reconstituted product is not administered immediately, storage shall not exceed 8 hours at room temperature (max. +25 °C). The reconstituted product should not be stored in the refrigerator.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze! Keep the vial in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Vials of colourless glass (Type II Ph. Eur.) sealed with a latex-free stopper (bromobutyl rubber), aluminium cap and plastic disc.

Pack with 1 g *(Figure 1)*

1. One vial containing 1 g human fibrinogen
2. Filter: Pall® Syringe Filter
3. Dispensing pin: Mini-Spike® Dispensing Pin

Figure 1

6.6 Instructions for use, handling and disposal

General instructions

- Reconstitution and withdrawal should be carried out under aseptic conditions.
- Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.
- The solution should be almost colourless to yellowish, clear to slightly opalescent and of neutral pH. Do not use solutions that are cloudy or have deposits.

Reconstitution

- Warm both the solvent and the powder in unopened vials to room or body temperature (not above 37 °C).
- Haemocomplettan should be reconstituted with water for injections (50 ml for 1 g, not included).
- Wash hands or use gloves before reconstituting the product.
- Remove the cap from the Haemocomplettan vial to expose the central portions of the infusion stoppers.
- Treat the surface of the infusion stopper with antiseptic solution and allow it to dry.
- Transfer the solvent with an appropriate transfer device into the infusion vial. Ensure complete wetting of the powder.
- Gently swirl the vial until the powder is reconstituted and the solution is ready for administration. Avoid strong shaking which causes formation of foam. The powder should be completely reconstituted within max. 15 minutes (generally within 5 to 10 minutes).
- Open the plastic blister containing the dispensing pin (Mini-Spike® Dispensing Pin) provided with Haemocomplettan (Figure 2).


Figure 2

- Take the provided dispensing pin and insert it into the stopper of the vial with the reconstituted product (Figure 3).


Figure 3

- After the dispensing pin is inserted, remove the cap. After the cap is removed, do not touch the exposed surface.
- Open the blister with the filter (Pall® Syringe Filter) provided with Haemocomplettan (Figure 4).

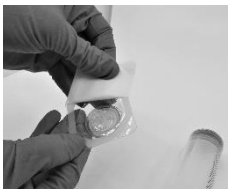
Figure 4

- Screw the syringe onto the filter (Figure 5).


Figure 5

- Screw the syringe with the mounted filter onto the dispensing pin (Figure 6).


Figure 6

- Draw the reconstituted product into the syringe (Figure 7).


Figure 7

- When completed, **remove the filter, dispensing pin and empty vial from the syringe,** dispose of properly, and proceed with administration as usual.
- Reconstituted product should be administered immediately by a separate injection / infusion line (see section 6.3).

- Take care that no blood enters syringes filled with product.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. DATE OF REVISION OF THE TEXT

Dec 2022